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RECORD OF ORAL HEARING

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex Parte FRANK A. SKRALY and MARTHA SHOLL

Appeal 2008-004223
Application 09/909,574
Technology Center 1600

Oral Hearing Held: May 14, 2009

Before TONI R. SCHEINER, RICHARD M. LEBOVITZ, and STEPHEN G. WALSH, *Administrative Patent Judges.*

APPEARANCES:

ON BEHALF OF THE APPELLANT:

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P R O C E E D I N G S

MS. BEAN: Good morning, Calendar No. 22, Ms. Pabst. Thank you.

JUDGE SCHEINER: Good morning. When you have a chance, if you could introduce yourself and your colleague for the record, please.

MS. PABST: Sure.

JUDGE SCHEINER: Whenever you're ready.

MS. PABST: I am Patrea Pabst and this is Dr. Oliver Peoples who is one of the inventors and representing the -- of the technology Metabolix.

JUDGE SCHEINER: If you have a business card also that would be helpful.

MS. PABST: Sorry?

JUDGE SCHEINER: If you have business cards with you that would be helpful.

MS. PABST: Oh, I do.

JUDGE SCHEINER: Whenever you're ready.

MS. PABST: Okay, thank you. Of course, we appreciate the opportunity to be here, and we really wanted an opportunity for Dr. Peoples to come and address any of your questions. It's complicated technology. It is their group that did the work in the primary reference which is a fairly abbreviated poster. We have comparative evidence here. It's kind of hard to follow one way or the other, but the bottom line here is that we have a piece of prior art, Skraly, that has been alleged to make obvious the claimed method. We have in Skraly a diagram of pathways by which one could convert from a cheap substrate to a valuable end product of polyhydroxyalkanoate. This is a business that Metabolix has been in since the technology was first developed at MIT in the 1980s. It's now commercially valuable technology. It's taken a long time. And this is one of

those cases when many times you look at something and you say well, this looks obvious, but, of course, the reality is it's not.

And I think one way, and I'm going to ask Dr. Peoples to explain it in more detail, but making subtle changes in technology can sometimes be very important commercially. If one looks at Table 1 in the application, and, again, Dr. Peoples is going to talk about this, but this I think is the most important place to, to look when he's talking. If you look at the method of Skraly, that's pretty much the method that gives a yield of about .7 percent for this one starting material with the pathway he describes. There are a lot of differences, but a major difference was the fact that you genetically engineer these organisms. You put the enzymes under control, not the enzymes in Skraly, but in particular, the aldehyde dehydrogenase and that changes that yield from .7 to about 25.3 percent.

JUDGE SCHEINER: May I interrupt you there? That -- in your Reply Brief and also in your appeal brief, you seem to make arguments that the claim required both a dioldiol oxidoreductase and an aldehyde dehydrogenase.

MS. PABST: It does.

JUDGE SCHEINER: And in the table that you referred to, it shows the highest yields with organisms genetically engineered to express both those enzymes. But the claim as we read it says selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase.

MS. PABST: Yes.

JUDGE SCHEINER: So literally it seems to say that you select an enzyme selected from a group of two.

MS. PABST: For genetic engineering, and this has to do with the amount of enzyme and, therefore, yield. Because the Examiner is correct, for example, that E. coli expresses an aldehyde dehydrogenase which is why when you look at this page that's entitled Polyols to PHA Precursors, you see aldehyde dehydrogenase. But when you look at which ones were incorporated genetically, it wasn't this enzyme.

JUDGE SCHEINER: Okay, but can you take a look at the claim because my question is it says selected from the group consisting of a reductase and a dehydrogenase. And I think the Examiner seems to be reading that it could require either a reductase or a dehydrogenase, and your argument seems to be directed to reading that it requires both of those enzymes.

MS. PABST: We read this claim as having -- the organisms having the enzymes to make the end product from these monomers. Some of these organisms will endogenously express one or both of the enzymes in that Markush group. The Markush group is specific to which ones must be genetically engineered.

JUDGE SCHEINER: But it's the Markush group, so generally through a Markush group as I understand it, you only need to select one to satisfy --

MS. PABST: To be genetically engineered, yes.

JUDGE SCHEINER: Okay, so you --

MS. PABST: To be genetically engineered to produce it and that is because -- in fact, if you were to just look, like I said, at Skraly, there is aldehyde dehydrogenase. It's not genetically engineered. And that amount makes a huge difference in the yield and, therefore, the commercial value of the technology. There's also no genetic engineering in Skraly of diol oxidoreductase. I'm sorry.

JUDGE SCHEINER: I believe there is. I believe that, at least looking at the figure on page 9 of 11, it seems to indicate that you would have the dehydrotase (phonetic spelling) and the oxoreductase genetically engineered into the -- which would meet the Markush limitation of the claim because it has no reductase there. And the dehydrogenase appears not to be genetically engineered, but the claim doesn't exclude that.

MS. PABST: I'm going to let Dr. Peoples because I'm not a good enough biochemist to get into this and I think we did explain our position pretty well in writing, but what I'd like Dr. Peoples to do is take and explain this technology and what's in here because they published it.

DR. PEOPLES: Yes, so fundamentally what was in the disclosure that -- presentation at a meeting by one of the technical -- technology was a description of some of the monomers that had been incorporated into PHA polymers and an indication of where some of those monomers had came from in terms of feed stocks that went in. And that's the table that describes what has been done generally, and so that's where the range of monomers in, in the Skraly reference came from. They were monomers that either had been demonstrated or had been demonstrated by other scientists in the field.

That was the start -- the, the science in this particular presentation really reflected around the 1,3 diol and the 1,2 diol and their incorporation into 3-hydroxypropanenic acid and into 3-hydroxypropanenic whey which was then condensed with another molecule to form another monomer 3-HP. So, I agree with you actually that it does talk about the 1,3 propanediol oxidoreductase, it talks about -- hydratase, it talks about the use of B-12 for controlling all of these things. It's silent on where the enzymes or genes for all the -- hydrogenase came from. As I read it indicates that it's coming from a nitro gene present in the organism and that, that seems to be the case. But what is not in here is the fact that when one looks at a range of different organisms, different organisms are likely to have different enzyme activities based on their genetic background. What we found, for example, and is illustrated in Table 1 is that the aldehyde dehydrogenase that is present in E. coli K-12 is clearly completely inadequate for the purpose of generating the full HB from 1-4 diol.

JUDGE SCHEINER: Scientifically, we understand that, and we did look at the table and we did see that the yields were much higher when you genetically engineered with both those enzymes. But the issue that we're talking about is what's in the claim, and the claim for example doesn't require that any particular yield is achieved, and it also doesn't require that both those enzymes are genetically engineered. If it did require that the reductase and the dehydrogenase were genetically engineered, that would be consistent with what you're arguing now.

MS. PABST: That is, in fact, Claim 8. I mean Claim 8 is where both are put in. There are organisms where you could have just one of those two enzymes that are added and I think -- take for a second and talk about the molecular weight, I think that's important, and about the process and a couple of other issues.

DR. PEOPLES: Yes. The issue with these, the issue with this use of diols and alcohols in general feeding through microbes is they do get processed through aldehyde intermediates typically. This is true of, for example, the 1,3 -- demonstrated in Skraly. It's also absolutely true in the production of virtinol [phonetic spelling] which is a major biofuel of interest generally. The evidence seems to indicate that they're all essentially hitting on an issue of controlling the level of intermediates. The aldehydes tend to be very toxic to the cells. It's very unpredictable which aldehydes will be toxic at what levels, and that depends on some knowledge which you may or may not have regarding how that aldehyde is converted to the next step. Is that really what's rate limiting, is it a co-factor limitation, it can be any number of things. What we found was that in some cases if you increase aldehyde dehydrogenase, that seems to basically solve the bottleneck and takes you from a .7 percent 4-HB up to a higher percentage 4-HB which is really the commercially relevant space -- and that actually is what we are commercializing, but in other cases, you'll find that it may be different. So, for example, although I don't have an example right here, in other cases, we may actually have adequate supply of the aldehyde dehydrogenase, but inadequate supply of the enzyme for converting the diol into the aldehyde.

What that results in is a build-up of the aldehyde -- of the diols in the fermentation feed stream, and because you can't get flow of carbon into the pathway, that then has other implications on basically the growth of these fermentations. And we have found this, this is actually what happens when you get this technology to an industrial scale, and you move it from essentially small -- glasses and now we're doing it on a several hundred thousand liter scale. And what you find is that it's very unpredictable how you control each of these stocks and you need to control all of it by tweaking the individual, if you like, enzymes to make sure that they're all expressed, not just expressed, but expressed at the right levels. So you cannot afford oversupply of a feed stock through the pathway and you cannot afford for the pathway to be blocked --

JUDGE LEBOVITZ: What happens when you get oversupply? Are you saying it can be lethal because --

DR. PEOPLES: It's lethal, yeah, you're basically -- you can -- you essentially get toxicity and the cells die in which case your fermentation stops. If you have an inadequate uptake in conversion of the diol, what happens is you're unable to actually make polymer and eventually the diol concentrations that you have have to be restarted to get enough -- through that. It essentially kills the cells because they're solvents basically. So, it's a tricky balancing act, that's the reality.

JUDGE SCHEINER: Can we back up to the polymer for just a second. Did you mention something about the size of the polymer?

MS. PABST: In the, in the claims, we have high molecular weight polymers, the weight average molecular weight of at least 300,000 Daltons. That goes to toxicity to kill off your system, the polymers aren't going to be as big. It also goes with supply of substrate, so you have to have -- and again, I think what Dr. Peoples was just talking about --

JUDGE SCHEINER: Is that an issue that's discussed in the brief?

MS. PABST: Oh, yeah, repeatedly.

JUDGE SCHEINER: And another question before we -- I'm sorry to interrupt, but I just wanted to get this down. Are there any claims that discuss the level of expression of the engineered -- of the enzyme data by genetic engineering?

MS. PABST: Well, if you look at Claim 1, and I think probably that's a good place to start. First off, of course, the diol that's in Skraly is not in Claim 1, this substrate's not in Claim 1. The second thing is that we have genetic engineering of the diol oxidoreductase and/or the aldehyde dehydrogenase, that's how I would read that Markush group. And then we have --

JUDGE SCHEINER: Does the claim actually require the presence of a certain diol substrate? It says that it has to be --

MS. PABST: Which can convert diols into these monomers. So -- I mean the diol will determine what monomer it's converted into. So, the answer is yes, I mean you can work either way. You can't --

JUDGE SCHEINER: Well, it has to be capable of it and something in there -- you have to get these polymers, the 300,000, out at the end of --

MS. PABST: Right, so you, you can't have the toxicity -- you must have an appropriate amount of substrate to get polymers of those molecular weights. You only can get appropriate amounts of the substrate if you have enough of one of these two enzymes to avoid the -- both to do the conversion to get enough substrate that will be polymerized in those high molecular weight polymers, and secondly, the avoid the toxicity issue where you get a build-up of these intermediates.

DR. PEOPLES: I think just one other point I would make is that the, the presence of aldehydes even in the chemical -- in chemical polymerization processes of polyesters, that's a big issue because you get chain termination and that reduces your molecular weight which reduces the use of the material. And this happens in PET, it happens in PBT, it happens in pretty much all the polyesters. And so you'll often see in most cases that they work pretty hard to make sure they don't build up these even very minor components. And it's turning out to also be a big issue for bio-based production of monomers because although you get, for example, Dupont's 1,3 propanediol technology, although you do make that material a very high concentration, small amounts of other derivatives of that can really mess up the polymerization and hence the use of the compound. You have to -- even --

MS. PABST: The prior art doesn't disclose molecular weights, so you say well, it's silent as to molecular weight. But because it specifically does not disclose genetic engineering of the aldehyde dehydrogenase, if you look at the page, it specifically says dehydrotase and oxydoreductase are then

imported into E. coli. We know that they haven't added the aldehyde dehydrogenase which would result in build-up of these toxic molecules. These are going to limit both the molecular weight and the yield. So you're not going to get what's claimed at a minimum as to molecular weight because of the build-up of the toxic intermediates because he doesn't recognize the importance of genetically engineering one or both of these to get that molecular weight. And simply, this very early, and it's a theoretical pathway. The unpredictability of the pathway is shown by this graph here where we look at what's produced -- do you want to explain that?

JUDGE LEBOVITZ: Is that the PH --

DR. PEOPLES: The PHBB, if you look at the PHBB as a result, although, although he is basically doing exactly the same polymer experiments he has done with the 1,3 diol that he's doing with the 1,2 diol to make PHBB, you see the HB level really doesn't increase. In fact, you also see that the PHBB level basically flattens
out -- but it doesn't block --

MS. PABST: That's this one.

DR. PEOPLES: In other words, it's not controllable, it's not predictable, it's not clear why. He does explain one theory as to why not with a case related to the need in that pathway for a thiolase (phonetic spelling) enzyme. We have that thiolase enzyme present in ours, and it clearly doesn't solve the problem in example --

MS. PABST: The Table 1.

DR. PEOPLES: -- Table 1 --

MS. PABST: So, the thiolase was not the solution.

DR. PEOPLES: It's simply not predictable how, how to optimize these combinations of enzymes, whether they can be endogenous, genetically engineered, whatever, to actually get to something that actually practically works. It's just, you know, unpredictable.

MS. PABST: Not, not from this, I mean when they actually show that you have to balance the level of those two enzymes so that you have adequate substrate, you don't build up toxic intermediates, you get these polymers with the molecular weight. It is a functional effective amount limitation in the sense that you must produce high molecular weight polymer. That means it can't stop due to build of the aldehydes, and that goes, of course, to the aldehyde dehydrogenase which is exactly what happens with this prior art which is shown by the comparative evidence in Table 1 with the .7 percent. We don't have that molecular weight in that table, we just have the yield. The yield is very, very low. It's about 1/30th to a 1/40th of the yield when you have the aldehyde dehydrogenase, but when you shut it down that early, you're not going to have long high-molecular weight polymer chains. So, you're not only going to have a low yield, but you're going to have low molecular weight as well.

JUDGE LEBOVITZ: Well, where, where's that evidence? You just said that the table doesn't have the molecular weight in it, so how do we know from that -- and I just want to point out I understand your argument, but Claim 1, at least, does not limit it to having both those engineered

enzymes in there. So, as long as you can get a little polymer with that high molecular weight, the claim limitation would be met.

MS. PABST: Can you answer that? This is not a question actually that was raised before.

DR. PEOPLES: Yeah, so I guess the question would be that if you just get a tiny amount of the polymer of the light molecular weight, does that count? Again, there's really no commercial value, you know. And I think there's probably some way to address that issue, but I'm not --

MS. PABST: I mean you could go measure it, but I don't think -- it hasn't been raised, so it wasn't determined.

DR. PEOPLES: Yeah, so, you know, what we do know is that if you look at Table 1, we talk about the percentage polymer in the cells, the dry percent dry cell weight. That's an indicative measure of the commercial utility of a particular process. Frankly, if you're making more cell mass than you have polymer, as is sometimes the case, that, that's kind of an issue, it's an economic issue. So I think my own view is you can make tiny amounts of something, but it doesn't really get you to something that's of any commercial value.

MS. PABST: Well, invention resides in -- and in this case, what was the invention. The invention was taking these pathways and actually determining the critical limiting factors. It happens to be those two enzymes. You can pick an organism that has an adequate amount of one, you can pick an organism with an adequate amount of the other, but you've got to take and balance the missing or inadequate amount of the other

enzyme which would depend on what you started with in order to get the high yields of these high molecular weight polymers which are critically important for their mechanical end property. That's the valuable polymer from a very cheap starting material. This doesn't get you there. It doesn't even talk about yields. It doesn't talk about molecular weight. What it instead shows is that if you take a couple of enzymes, which are not the ones we're claiming, the two critical weight-limiting factors, and you put them into an organism which happens to have a very, very small amount endogenously of the other enzyme, the aldehyde dehydrogenase, is that you'll get something, but the invention is making something that's commercially useful. Thirty to 40 percent yield in polymer is a huge difference. Yes, it will turn on what you start with as your background organism, but that's -- it's understanding that those are your rate -- that the aldehyde is going to be rate limiting and molecular weight limiting, and that, you know -- yes, you can come back and say yeah, we know that it's going to be limiting as far as the molecular weight because of what's known of polyesters, but that's not in any of this prior art because nobody made the connection from engineering these organisms to express the right amount of these enzymes not to have that build-up. Once you got the build-up, yeah, the system shuts down, you get a small amount of polymer. It is likely that it's a very small molecular weight because of the importance of not knowing the difference in what's going to be weight controlling. This was a long -- the company's been around a long time now.

DR. PEOPLES: Don't rub it in.

MS. PABST: Well, okay, we won't go there. So, what seems so obvious in hindsight because you can explain your results doesn't make it obvious. Until they actually did these studies, compared those results, and looked at what was in Table 1, it wasn't clear which of these was an endogenous enzyme going to be sufficient. If you look at Skraly, that's what he assumes, and he looks at other enzymes as being what's important here, and the fact that he says well, you have to have this co-enzyme B-12 to turn it on and that's how I'm going to get there.

JUDGE LEBOVITZ: In your specification on page 14 and lines 1 through 6 in the Appeal Brief --

MS. PABST: I'm sorry, where are you?

JUDGE LEBOVITZ: Well, go to your Appeal Brief, page 8 -- your Reply Brief, excuse me.

MS. PABST: Okay, hang on a second.

JUDGE LEBOVITZ: Yes, take your time.

MS. PABST: I had all the wrong things. Okay, Reply Brief where?

JUDGE LEBOVITZ: Page 8.

MS. PABST: Got it, okay.

JUDGE LEBOVITZ: And you refer to an example in the spec on page 14, lines 1 through 6 and maybe Dr. Peoples -- I just want your verbal discussion of that for a few minutes.

MS. PABST: Okay, page 14.

JUDGE LEBOVITZ: We're referring to specification lines -- page 14, lines 1 through 6. And I think what you're saying is that we, we compared

what Skraly did to what we did and the yields are, it looks like four times different.

MS. PABST: In this particular -- that's not, that's not the same. That's not the same as Skraly, though.

JUDGE LEBOVITZ: That's what I'm asking you. The Skraly method was 25 percent according to -- was 25 percent of the claimed method, that's a different Skraly? What was that compared to?

MS. PABST: Okay. Example 3 shows that PHA production using 1-4 butane diol in E. coli using the Skraly method which is where they're not adding -- they're not -- okay, I see, I see your question.

DR. PEOPLES: They're only using one end.

MS. PABST: Yeah, they're not --

DR. PEOPLES: They're not using ADH.

MS. PABST: Skraly method is where you -- yes, okay. You've got it now?

DR. PEOPLES: I know what it is, but all I can truly tell you is that the difference between these two -- I know what this is. The point is the difference between these two examples is one is making a co-polymer which is Table, Table 1, basically -- it results with a .72.925.3, and this is making a whole new follow-up. Now, clearly there's a difference in the level achieved in this particular individual experiment, that's absolutely correct. How relevant it is to the point is not clear to me, the issue being that if you're only making the 4-HB and you don't have any other metabolism going on to make this 3-HB, things will change again. Again, it just goes to the fact that

there's a lot of work has to go into making these actually useful. So, -- that experiment and these are -- yeah -- a low D of 3.9, again we're talking a very small samples. This is not -- essentially tests two results and so there's going to be variation in there as well. But I don't think it speaks to the major issue which is when you started and made co-polymers, you changed the game again. You add another level of complexity because now not only do you have to take the diol to the monomer 3-1-4 or 4-HB, but you also have to provide the other co-monomer at the same time. And to actually make a polymer that's useful commercially, you have to also be able to control all that. And that's part of what this particular invention and these examples in Table 1 allowed us to do. Essentially, the commercial technology is -- actually encompasses these genes and this genetic system and it makes a co-polymer where we can regulate the level of the co-monomer which is not disclosed here, but when you put it into fermenters, you're able to now control the level of the co-monomer by feeding one probutane diol so that not only can they produce 5 percent 4-HB, but 10 percent, 20 percent, 30 percent. And so until we had that, we couldn't control all this.

JUDGE SCHEINER: Okay. We're going to have to wrap this up here. I think we do understand it. Is there any other issue that you wanted to quickly --

MS. PABST: Yeah, I think, I think, again, our Appeal Brief and Reply Brief I think spell out we don't think Skraly discloses the claimed elements. We do think we have unexpected results. We think that there was an additional step that's simply not in the prior art which was the recognition

of the importance of having adequate and controllable amounts of one or both of these enzymes to control the levels of what the substrates were able to convert to so that you avoid toxicity so that you got polymers of sufficiently high molecular weight. If it shut down early, it doesn't get you to the molecular weight that's in the claims. And you could select -- the reason it's done as a Markush with those two enzymes is because you could select an enzyme that had an adequate amount of one. You wouldn't have to genetically engineer it. So, we put it in there that way because otherwise it's a meaningless claim if you must genetically engineer whichever one of those is not sufficient. But if we require both, then somebody just takes an endogenous strain with an endogenous amount of one of those enzymes, puts in genetically the other, then they can get there. And that would, of course, obviate the value of this technology, technology which has taken a lot of years and money to develop.

JUDGE SCHEINER: Okay, do you have any further questions?

JUDGE LEBOVITZ: No, thank you.

JUDGE SCHEINER: Thank you for coming in.

MS. PABST: You're welcome.

(Whereupon, the hearing concluded at 9:50 a.m. on May 14, 2009.)